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Title: Nonequilibrium Statistical Mechanics: potential applications in biology

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Nonequilibrium Statistical Mechanics: potential applications in biology

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Los Alamos National Laboratory

March 7, 2014

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Talk Outline

The Challenge

Mathematical Formulation

Approximate Solutions

- Effective Action
- Effective Potential
- Entropy-based Closures and Equation-Free Methods

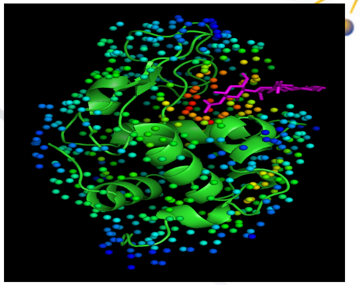
Future Directions

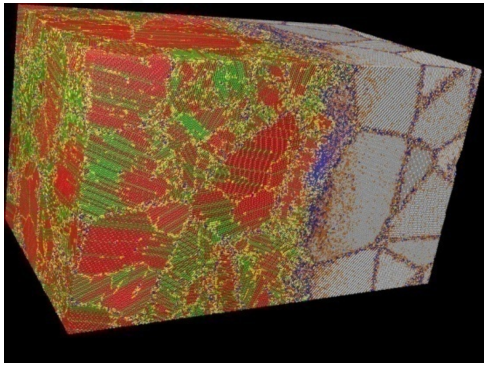
Challenge: Fast, accurate simulations of complex large-scale systems with a ***quantified, predictive capability***

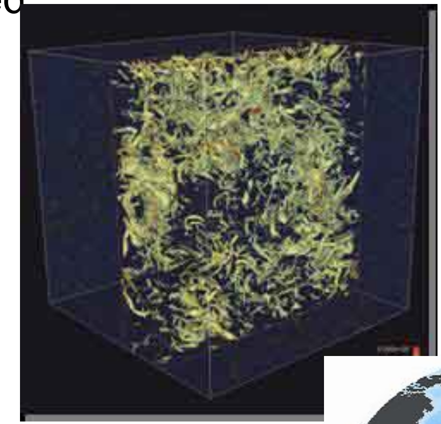
- Many degrees of freedom
- Strongly coupled / nonlinear interactions
- Multi-scale (perhaps with no scale separation)
  - Turbulence
  - Critical Phenomena
- Many realizations needed
  - Data assimilation / particle filtering
  - Uncertainty quantification
  - Design / optimization
- Real-time capability may be needed
  - Control
  - Tracking
  - Rapid Decision making (socio-technical systems modeling, risk assessment)

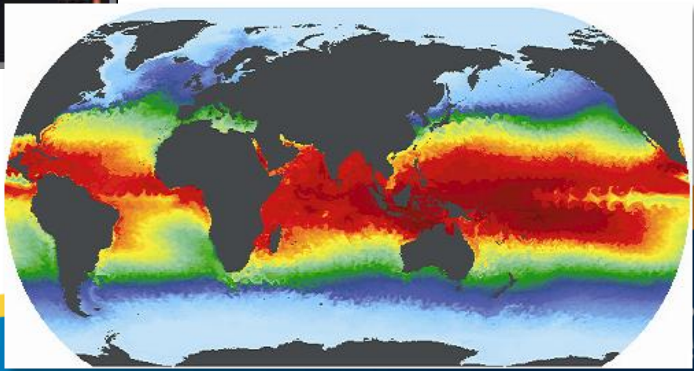
Example Applications

- Biophysical / Biochemical Processes
  - Stochastic systems modeling (a la Gillespie), Probabilistic Boolean Networks etc.
  - Systems of Stochastic ODE's
  - Molecular Dynamics
- Materials Modeling
  - Molecular Dynamics / Accelerated MD
  - Kinetic Monte Carlo
  - Finite Elements
- Fluid and Plasma Turbulence
  - Navier-Stokes
  - Euler
  - Magnetohydrodynamics
- Climate
  - Coupled Atmosphere/Ocean Models









All statistical information is contained in solution to the Liouville/ Kolmogorov equations

- General Class of Dynamical Systems

$$\dot{\mathbf{X}} = \mathbf{U}(\mathbf{X}(t), \mathbf{N}(t), t)$$

Evolution Equations such as
PDEs, ODEs,
Integrodifferential equations…

Unknown parameters
Random Forcing
Neglected Degrees of Freedom

$$\mathbf{X}_{t+1} = \mathbf{U}_t(\mathbf{X}_t, \mathbf{N}_t)$$

Dynamical Maps

Liouville or Kolmogorov Equation:

$$\partial_t P = \mathcal{L}^*(t) P$$

Full (Probability)
Distribution Function

Evolution Operator

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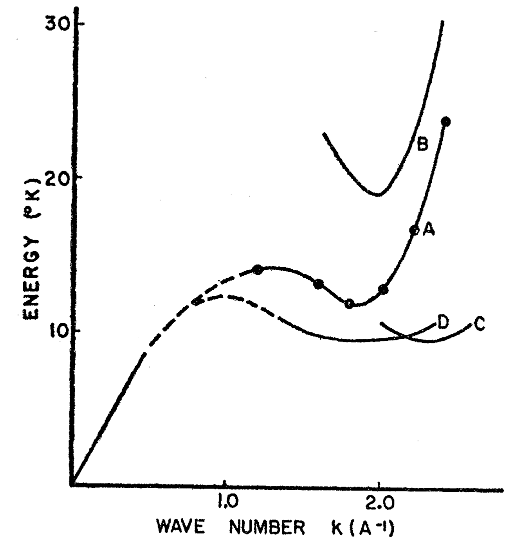
How to get information from these equations … when you can't solve them

- Partial differential equations in state-space (large or infinite dimension)!
- Could solve problem by ensemble over stochastic elements / initial conditions. Even one realization could be prohibitive
- Replace Liouville/Kolmogorov equations by small set of PDE's or ODEs
  - Cast problem variationally
  - Low Order statistical moments of the solutions
  - Must approximate higher-order moments in terms of lower order moments e.g.
    - Example the Boltzmann equation replaces two particle distribution functions as products of single particle distribution functions
  - Expert Knowledge / Empirical data / Physical Insight are key

The Rayleigh-Ritz variational approach

“The great virtue of the variational treatment, ‘Ritz’s method’, is that it permits efficient use in the process of calculation, of any experimental or intuitive insight which one may possess concerning the problem which is to be solved by calculation…” (J. von sNeumann)



J. von Neumann, “Use of variational methods in hydrodynamics” (1945), in: Collected Works. (Pergamon Press, New York, 1963).

Feynman, RP and Cohen, M, Energy Excitations in Liquid He Physical Review, **102**, 1956.

Pros/cons of the statistical moment closure and variational approaches

- Pros
  - Greatly reduced complexity of governing equations
  - Resulting equations may be easier to solve
    - Typically deterministic
    - Less stiff (fast degrees of freedom may be averaged out?)
- Cons
  - Quality of approximation may not be easy to evaluate (e.g., non-Self Adjoint evolution)
  - Poor closures/trial wave funcstions lead to poor approximations and/or poor convergence

Three Variational Approaches: from Quantum Field Theory / Nonequilibrium Statistical Mechanics)

- Effective Action
- Effective Potential
- Entropy-based closures and Equation Free methods

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Effective Action

Vector-valued random process Z(t)

Cumulant generating functional

$$W_Z[\mathbf{h}] = \log\langle\exp\left(\int_{t_i}^{t_f} dt\ \mathbf{h}^\top(t)\mathbf{Z}(t)\right)\rangle$$

$$C_{i_1\cdots i_n}(t_1,...,t_n) = \left.\frac{\delta^n W_Z[\mathbf{h}]}{\delta h_{i_1}(t_1)\cdots\delta h_{i_n}(t_n)}\right|_{\mathbf{h}=\mathbf{0}}$$

$$\Gamma_Z[\mathbf{z}] = \max_{\mathbf{h}}\{<\mathbf{h},\mathbf{z}> - W_Z[\mathbf{h}]\}$$

$$<\mathbf{h},\mathbf{z}>:= \int dt\ \mathbf{h}^\top(t)\mathbf{z}(t)$$

K. Symanzik, Commun. Math. Phys. 16, 48 (1970)

J. M. Cornwall, R. Jackiw, and E. Tomboulis, Phys. Rev. D 10, 2428 (1974)

Connection to Large Deviations Theory

$$\Gamma_{i_1 \dots i_n}(t_1, \dots, t_n) = \frac{\delta^n \Gamma_Z[\mathbf{z}]}{\delta z_{i_1}(t_1) \cdots \delta z_{i_n}(t_n)}\bigg|_{\mathbf{z}=\overline{\mathbf{z}}}$$

Rate function in large deviations theory

$$\overline{\mathbf{Z}}_N(t) := \frac{1}{N} \sum_{n=1}^{N} \mathbf{Z}_n(t)$$

$$P\left(\overline{\mathbf{Z}}_N(t) \approx \mathbf{z}(t) : t_i < t < t_f\right) \sim \exp\left(-N \cdot \Gamma_Z[\mathbf{z}]\right)$$

Variational Formulation of Effective Action for Classical Dynamics

$$\partial_t \mathcal{P}(\mathbf{x},t) = \hat{L}(t)\mathcal{P}(\mathbf{x},t) \qquad \partial_t \mathcal{A}(\mathbf{x},t) = -\hat{L}^*(t)\mathcal{A}(\mathbf{x},t)$$

$$\Gamma[\mathcal{A},\mathcal{P}] := \int_{t_i}^{t_f} dt \ < \mathcal{A}(t), (\partial_t - \hat{L}(t))\mathcal{P}(t) >$$

$$\Gamma_Z[\mathbf{z}] = \mathrm{st.pt.}_{\mathcal{A},\mathcal{P}} \Gamma[\mathcal{A},\mathcal{P}]$$

$$< \mathcal{A}(t), \mathcal{P}(t) >= 1$$

$$< \mathcal{A}(t), \hat{\mathbf{Z}}(t)\mathcal{P}(t) >= \mathbf{z}(t)$$

G. L. Eyink, Phys. Rev. E 54, 3419 (1996)
GL Eyink, FJ Alexander, Physical review letters 78 (13), 2563

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Properties of the Exact Effective Action

$$\Gamma[z] \geq 0, \qquad \Gamma[\overline{z}] = 0$$

$$\lambda\Gamma[z_1] + (1-\lambda)\Gamma[z_2] \geq \Gamma[\lambda z_1 + (1-\lambda) z_2]$$

- Realizability – if approximate Effective Action is nonconvex, then it is a bad predictor of fluctuations about mean.
- The method proposed should result in a statistically-improved predictive ability, i.e. a greater fraction of closure predictions which pass the "screening" should be accurate.

Potential Applications of the Effective Action

- Response Functions for random variables in systems biology– coupled stochastic ODE’s
- Control Theory – for a given controller calculate the effective potential
- Data Assimilation and Model selection
- What is the effective action for various systems– healthy vs diseased?

Effective Potential: Steady State

$$V[\mathbf{z}] = \lim_{T\to+\infty} \frac{\Gamma[\mathbf{z}_T]}{T}.$$

$$\overline{\mathbf{z}}_T \equiv \frac{1}{T}\int_0^T dt\,\mathbf{z}(t).$$

$$\mathrm{Prob}(\overline{\mathbf{z}}_T \approx \mathbf{z}) \sim \exp(-TV[\mathbf{z}])$$

$$\mathcal{H}[\Psi^R,\Psi^L] \equiv \langle \Psi^L, \hat{L}\Psi^R\rangle.$$

$$V[\Psi^R,\Psi^L] = -\mathcal{H}[\Psi^R,\Psi^L]$$

$$\langle \Psi^L, \Psi^R\rangle = 1$$

$$\langle \Psi^L, \hat{\mathbf{Z}}\Psi^R\rangle = \mathbf{z}$$

Properties of the Exact Effective Potential

$$
\begin{aligned}
&\text{(i)} \quad (\textit{positivity}) && V[\mathbf{w}] \geqslant 0 \\
&\text{(ii)} \quad (\textit{unique minimum}) && V[\mathbf{w}] = 0 \quad \text{iff} \quad \mathbf{w} = \bar{\mathbf{w}} \\
&\text{(iii)} \quad (\textit{convexity}) && \lambda V[\mathbf{w}] + (1-\lambda)\, V[\mathbf{w}'] \\
& && \quad \geqslant V[\lambda \mathbf{w} + (1-\lambda)\, \mathbf{w}'], \qquad 0 < \lambda < 1
\end{aligned}
$$

Reject nonphysical closures:
A closure leading to and approximate potential V(w) which does not satisfy all realizability conditions (i)-(iii) must be rejected.

Effective Potential: Kramers' problem

- Variational Formulation

Driven/damped dynamics in a cosine potential

$$\ddot{x} + \gamma \dot{x} + V_0 \sin x = F + \Gamma(t)$$

$$\langle \Gamma(t) \Gamma(t') \rangle = 2\gamma\Theta\,\delta(t - t')$$

$$\frac{\partial}{\partial t} Pt = -\frac{\partial}{\partial x}(v P_t) + \frac{\partial}{\partial v}\left[\left(\gamma v + V_0 \cos x - F + \gamma\Theta \frac{\partial}{\partial v}\right) P_t\right] \equiv \hat{L} P_t$$

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Approximate Effective Action for Kramers' problem

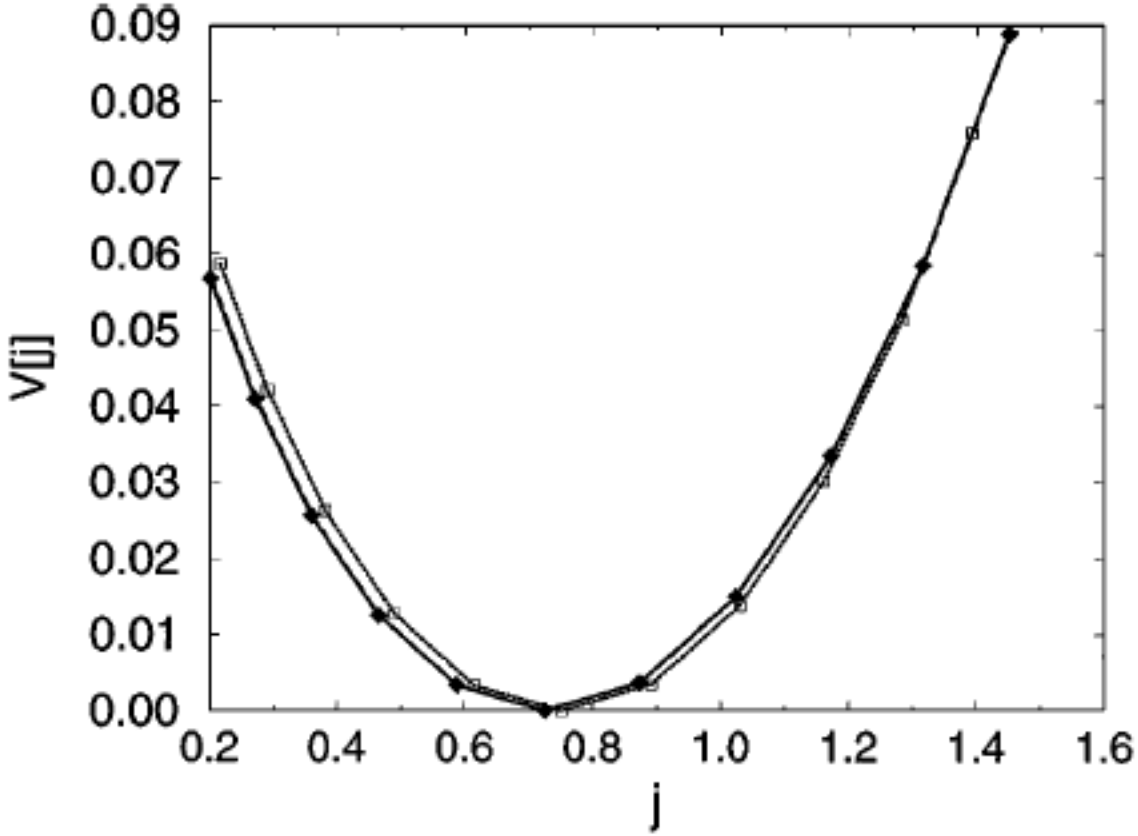

FIG. 1. Approximate effective potential $V[j]$ for $N = 4$, $P = 5$ (□), $N = 6$, $P = 6$ (+), and $N = 10$, $P = 8$ (◇).

Exact Effective Potential vs Converged Rayleigh-Ritz

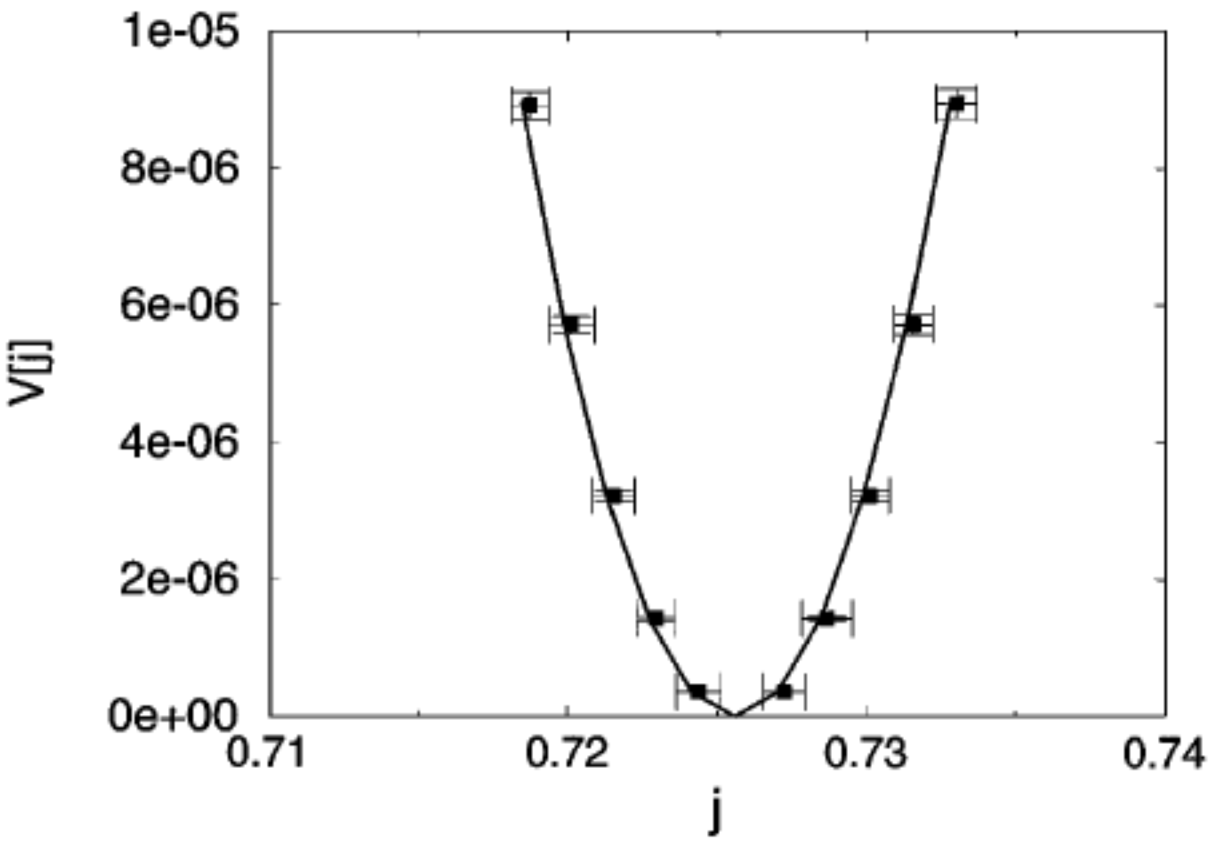

FIG. 2. Potentials $V[j]$ for DNS (with errorbars) and the $N = 10$, $P = 8$ Rayleigh-Ritz calculation (solid line).

Effective Potential: possible applications

- What is the probability that the time T average of random variables of interest does not exceed a specified amount? Uses in therapeutics?
- What are the probabilities of rare excursion?

Equation Free methods to overcome PDF closures challenges.

- PDF closures may themselves be too difficult / complicated to write down
  - Even with computer algebra systems
  - Global Climate models are an example of this
- Models are often updated – require complete reformulation of closure
- May be impossible to derive closure equations analytically/ in closed form (especially true if PDFs are nonGaussian – most useful closures are non-Gaussian)
- May only have a code (no equations!) – cannot derive closure equations in that case
- Need a robust approach to general closure problem
- Build on ideas of I. Keverkidis

Let's get slightly more specific

Markov Process (Brownian Motion, Poisson…)

$$\dot{\mathbf{X}} = \mathbf{U}(\mathbf{X}(t), \mathbf{N}(t), t)$$

$$d\mathbf{X} = \mathbf{U}(\mathbf{X}, t)dt + \sqrt{2}\mathbf{S}(\mathbf{X}, t)d\mathbf{W}(t)$$

Ito Stochastic Differential Equation

$$\partial_t P = \mathcal{L}^*(t)P$$

Forward Kolmogorov Equation; generator of Markov Process $\mathcal{L}^*$

$$\mathcal{L}^*(t)\psi(\mathbf{X}) = -\nabla_{\mathbf{X}} \cdot (\mathbf{U}(\mathbf{X}, t)\psi(\mathbf{X})) + \nabla_{\mathbf{X}}^2 : (\mathbf{D}(\mathbf{X}, t)\psi(\mathbf{X}))$$

$$\partial_t P + \nabla_{\mathbf{X}} \cdot (\mathbf{U}P) = \nabla_{\mathbf{X}}^2 : (\mathbf{D}P)$$

Fokker-Planck Equation –
Linear, Deterministic, possibly infinite dimensional

$$\mathbf{D}(\mathbf{X}, t) = \mathbf{S}(\mathbf{X}, t)\mathbf{S}(\mathbf{X}, t)^T$$

Diffusion Matrix from Noise Term

FJ Alexander, G Johnson, GL Eyink, IG Kevrekidis Physical Review E 77 (2), 026701

Now the Moment Equations

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$$\xi(\mathbf{X},t)$$

Select small set of relevant variables, order parameters
Simplify computation
Retain relevant "physics"…

$$\mu(t) = \int \xi(\mathbf{X},t) P(\mathbf{X},t) d\mathbf{X},$$

Take moments of FP equation

$$\dot{\mu}(t) = \int \dot{\xi}(\mathbf{X},t) P(\mathbf{X},t) d\mathbf{X}$$

Average over ensemble of original system
Not in general a closed form equation

$$\dot{\xi}(\mathbf{X},t) = \partial_t \xi(\mathbf{X},t) + \mathcal{L}(t)\xi(\mathbf{X},t)$$

$\mathcal{L}$ Adjoint of Kolmogorov Operator $\mathcal{L}^*$

Getting the reduced equation into a closed form

$P(\mathbf{X},t,\boldsymbol{\mu})$ Choose a PDF that is a function of the moments

$$\dot{\boldsymbol{\mu}}(t) = \mathbf{V}(\boldsymbol{\mu},t) \equiv \int \dot{\xi}(\mathbf{X},t)P(\mathbf{X},t,\boldsymbol{\mu})d\mathbf{X}$$

$P(\mathbf{X},t,\boldsymbol{\alpha})$ Another pathway – choose PDF to be specified by parameters

$\boldsymbol{\alpha}=\boldsymbol{\alpha}(\boldsymbol{\mu},t)$

Analogy to choosing temperature instead of energy
Canonical instead of Microcanonical

Equivalent representation given invertible
Several ways to transform between moments and parameters

$P(\mathbf{X},t,\boldsymbol{\alpha}(\boldsymbol{\mu})(t))$ Goal: that parametric PDF approximates solution to Kolmogorov

Switch gears: to the Equation-free approach

Pioneered by I. Kevrekidis --see Comm Math Science **1** 715 (2003)

Closed, but we still need the dynamical vector field

$$\dot{\mu}(t) = \mathbf{V}(\mu, t) \equiv \int \dot{\xi}(\mathbf{X}, t) P(\mathbf{X}, t, \mu) d\mathbf{X}$$

Key Observation: Numerical computations involving closure equations do not require closed formulas

Where rubber meets the road!
1.) can make practical implementation challenging
2.) want method robust to changes in codes/models
3.)want method that can work with complex PDFMCs

Equation-free approach: how it works:

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Sample an ensemble from Closure Ansatz

$$\mathbf{X}(t) \qquad P(\mathbf{X},t;\alpha)$$

$\downarrow$

Evolve sample for short time (could even be a code or black box)

$$\mathbf{X}(t+\delta t) \longrightarrow \begin{matrix}\alpha \\ \mu\end{matrix}$$

Moments/ parameters at beginning and end of interval δt.

$\downarrow$

$$\dot{\mu} \qquad \mathbf{V}(\mu,t)$$

$$\mathbf{X}(t) \qquad \dot{\mu}(t) = \mathbf{V}(\mu,t) \equiv \int \dot{\xi}(\mathbf{X},t)P(\mathbf{X},t,\mu)d\mathbf{X} \qquad \Delta t$$

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Projective Euler Method (could use other integrators)

$\boldsymbol{\mu}(t)$ Start with specified moments

$P(\mathbf{X},t;\boldsymbol{\alpha}(t))$ Generate an ensemble of fine-grained systems via PDF ansatz

$\mathbf{X}(t)$ Evolve via original dynamics $\mathbf{X}(t+\delta t)$

Calculate new moments $\boldsymbol{\mu}(t+\delta t)$

$\dot{\boldsymbol{\mu}}$ From old and new moments (precisely the RHS of explicitly unavailable dynamics)

$$\boldsymbol{\mu}(t+\Delta t)=\boldsymbol{\mu}(t)+\Delta t\left[\frac{\boldsymbol{\mu}(t+\delta t)-\boldsymbol{\mu}(t)}{\delta t}\right]$$

REPEAT

Comments:

- Why not just solve original equation for moments (why make a closure approximation at all?)
- Fine scale dynamics may be stiff / closure equation usually less stiff (compare Molecular Dynamics with Navier Stokes)
- Moments usually much smoother in space and time

t_0+T

Savings

Fine Grained Model

Projective Integration

$O(T/\delta t)$

$O(T/\Delta t)$

$O(\Delta t/\delta t)$

$\Delta t \gg \delta t$

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Putting it all together…

Marrying statistical moment closures with the equation free method

Concrete Example: Nonlinear Reaction Diffusion

$$\frac{\partial \phi(x,t)}{\partial t} = D\Delta\phi(x,t) - V'(\phi(x,t)) + \eta(x,t)$$

Time Dependent Ginzburg-Landau

$$\langle \eta(x,t)\,\eta(x',t')\rangle = 2kT\,\delta(x-x')\,\delta(t-t')$$

$$V(\phi(x,t)) = \frac{1}{2}\phi^2(x,t) + \frac{1}{4}\phi^4(x,t)$$

Let's work above T_c

$$P_*[\phi] \propto \exp(-H[\phi]/kT)$$

Gibbs Distribution / Invariant Measure

$$H[\phi] = \int \left[\frac{1}{2}D|\nabla\phi(x)|^2 + V(\phi(x))\right]dx$$

More details

$$\bar{\phi}(t) = (1/V)\int \phi(x,t)\,dx \qquad \mu(t) = \langle \bar{\phi}(t) \rangle$$

$$\mu(t) = \langle \phi(x,t) \rangle$$

$$\frac{\partial \langle \phi(x,t) \rangle}{\partial t} = D\Delta \langle \phi(x,t) \rangle - \langle \phi(x,t) \rangle - \langle \phi^3(x,t) \rangle$$

$$\langle \bar{\phi}^3 \rangle \qquad \langle \phi^5 \rangle$$

$$P[\phi;\alpha] \propto \exp(-H[\phi;\alpha]/kT) \qquad H[\phi;\alpha] = H[\phi] + \alpha \int \phi(x)\,dx$$

More details

$$\xi[\phi] = (1/V)\int\phi(x)dx$$

$$\alpha(t) \to 0$$

$$P[\phi;\alpha(t)]$$

$$(\partial/\partial\alpha)[\alpha\mu - F(\alpha)] = \mu - \mu(\alpha)$$

$$P_*[\phi]$$

$$\alpha = \text{argmax}_\alpha[\alpha\mu - F(\alpha)]$$

$$\mu(\alpha) = \langle\xi\rangle_\alpha$$

$$F(\alpha) = \ln\langle\exp[\alpha\int\phi(x)dx]\rangle_*$$

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Discretized form

$$\phi(x,t+\delta t) = \phi(x,t) - \delta t[\phi(x,t) + \phi^3(x,t)] + \frac{D\,\delta t}{(\delta x)^2} \times [\phi(x+\delta x,t) - 2\phi(x,t) + \phi(x-\delta x,t)] + \sqrt{2kT(\delta t/\delta x)}N(x,t),$$

$$H_\delta = \frac{D}{2\,\delta x}\sum_{\langle x,x'\rangle}[\phi(x) - \phi(x')]^2 + \sum_x \delta x\left[\frac{1}{2}\phi^2(x) + \frac{1}{4}\phi^4(x)\right]$$

$$P_\delta[\phi;\alpha] \propto \exp(-H_\delta[\phi;\alpha]/kT)$$

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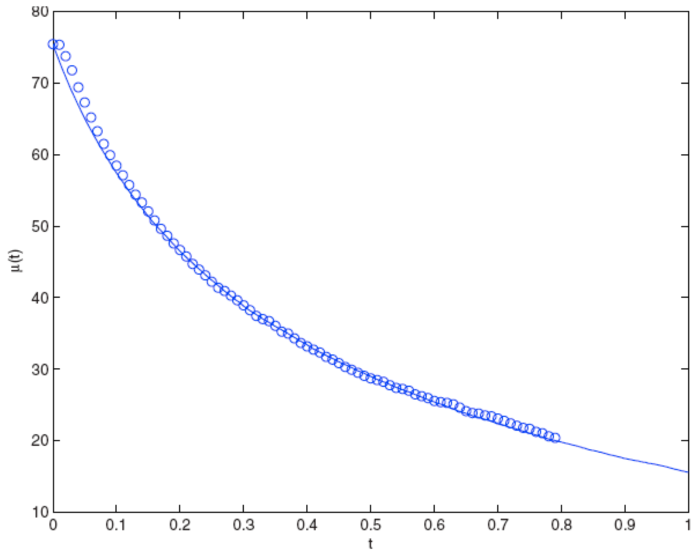
Integration Scheme

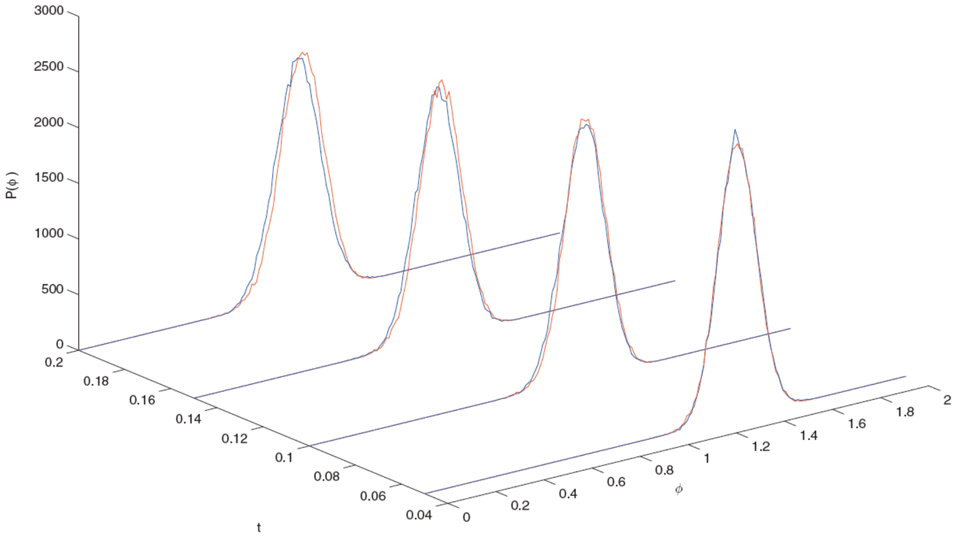
$$H_\delta[\phi;\alpha] = H_\delta[\phi] + \alpha \sum_x \delta x \phi(x)$$

$$\dot{\mu}_{app}(t) = [\mu(t+\delta t) - \mu(t)]/\delta t$$

$$\mu(t+\Delta t) = \mu(t) + \Delta t\,\dot{\mu}_{app}(t)$$

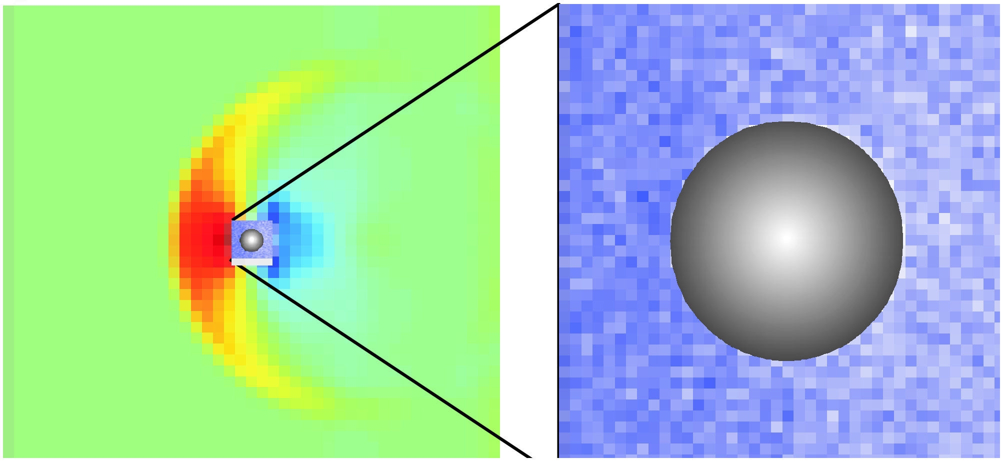
Mean (ensemble averaged) total field and PDF as a function of time





What would this look like for fluids and gases?

Track particles Molecular Dynamics
Direct Simulation Monte Carlo



Coarse Grain the system in space

Calculate density, momentum, energy in a cell

Update microscopic dynamics

Coarse Grain the system in space

Calculate density, momentum, energy in a cell

PDF Selection: Maxwell-Boltzmann: Euler
Chapman-Enskog Navier-Stokes

Update PDF

Repopulate fine grained model

Future Directions

- Apply methods to more challenging problems
- Plug and Play …Quickly Test Closure Ideas for
  - Materials
  - Optimal Filtering
  - *Biological Systems*
  - Climate
  - Turbulence
- Reinforcement Learning for closure development/ trial wave design
- OUQ / Error analysis / Robust formulation
- Applications to Stochastic Control / Value Function / Cost-to-go

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